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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HILL, KEVIN KAI	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 12/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/808,161	DIAS ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-32* is/are pending in the application.

4a) Of the above claim(s) *27,28,31 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/158,272.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *Mar 24, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Effective November 14, 2006, the Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Kevin K. Hill, Art Unit 1633.

Detailed Action

1. Applicant's response to the Requirement for Restriction, filed on September 25, 2006 is acknowledged.

Applicant has elected the invention of Group I, Claims 29-30, drawn to a method for manipulating the genome of a pathogenic Gram-positive bacteria comprising administering a prokaryotic beta recombinase and its specific target sequences.

2. Election of Applicant's invention(s) was made with traverse.

Applicant argues that it would not be unduly burdensome for the Examiner to examine all of claims 27-32 in this application as all of the claimed methods are directed to manipulation methods which employ prokaryotic beta recombinase.

The Examiner finds this argument unpersuasive and has explained in the Requirement for Restriction that the inventions encompass methodology that uses different starting materials and results in materially different products. Each method would require specific method steps not recited in the instant claims that are materially different for each host in which the general method is practiced.

MPEP §803 states that "If the search and examination of all the claims in an application can be made without serious burden, the examiner must examine them on the merits, even though they include claims to independent or distinct inventions."

In the instant case a serious burden exists since each limitation of the non-elected inventions, directed to transgenic plants and human gene therapy, requires a separate, divergent, and non co-extensive search and examination of the patent and non-patent literature. Further, a search and examination of all the claims directed to the embodiments involves different considerations of novelty, obviousness, written description, and enablement for each claim. In view of these requirements, it is the Examiner's position that searching and examining all of the

claims including limitations to transgenic plants and human gene therapy in the same application presents a serious burden on the Examiner for the reasons given above and in the previous Restriction Requirement.

The requirement is still deemed proper and is therefore made FINAL.

Amendments

Applicants' preliminary amendment, filed March 24, 2004 has been received and entered. Claims 1-26 have been cancelled. Claims 27-32 have been added.

3. Claims 27-28 and 31-32 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

4. Claims 29-30 are under consideration.

Priority

5. This application filed March 24, 2004, is a divisional of application 09/158,272, filed September 22, 1998, now US Patent 6,780,644, which claims benefit of provisional application 60/062,994, filed October 23, 1997. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120 is acknowledged.

Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). A certified copy of the foreign patent application (SE 9703663-6, filed October 8, 1997) has been filed on October 14, 1998 in parent application 09/158,272, filed September 22, 1998.

The subject matter of the instant invention is the use of prokaryotic beta recombinase in pathogenic and Gram-positive bacteria; whereas, the subject matter of the priority documents SE 9703663-6, 60/062,994 and 09/158,272 are directed to the use of prokaryotic beta recombinase

in eukaryotic cells. Specifically, a key-word search of the instant specification using the term "pathogenic" recited in Claim 29 fails to identify any use of the term. Similarly, a key-word search using the terms "Gram" or "Gram-positive" yields only the introductory identification of the host-range plasmid pSM19035 (pg 3, line 1). Thus, the instant invention is not supported by the disclosures of the priority documents. Accordingly, the effective priority date of the instant application is granted as the filing date of the instant application, March 24, 2004.

Information Disclosure Statement

Applicant has filed an Information Disclosure Statement on March 24, 2004. The references have been considered. The signed and initialed PTO Form 1449 has been mailed with this action.

Specification

6. **The disclosure is objected to because of the following informalities**: The specification contains sequence listings which do not have a SEQ ID NO: (see for example page 5; lines 3-4 and page 7; lines 18-19). The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

Appropriate correction is required.

The absence of proper sequence listing did not preclude the examination on the merits. However, for a complete response to this office action, applicant must submit the required material for sequence compliance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. **Claims 29-30 are rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a method for manipulating pathogenic and Gram-positive bacteria, the method comprising introducing prokaryotic beta recombinase and its specific target sequences in the pathogenic and Gram-positive bacteria. At issue for the purpose of written description requirements, are three points: a) "pathogenic and Gram-positive bacteria", b) "beta recombinase", and c) "specific target sequences". Each will be discussed in detail below.

Vas-cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus.

With respect to the genus of pathogenic and Gram-positive bacteria, as commonly understood in the art, a pathogen or infectious agent is a biological agent that causes disease or illness to its host, and includes both Gram-negative and Gram-positive bacteria. The term is most often used for agents that disrupt the normal physiology of a multicellular animal or plant (wikipedia, en.wikipedia.org/wiki/Pathogen, last visited on November 17, 2006). Thus, the subject matter in which the invention is claimed to be used embraces an enormous genus of human and non-human pathogenic prokaryotes. However, the specification does not teach what is the complete structure of any pathogenic bacterial species of the genus. Except for claiming that the bacteria could be Gram-positive, the specification does not teach what would be the structure of a species of the genus.

With respect to the genus of prokaryotic beta recombinases, the beta recombinase encoded by the plasmid pSM19035, derived from *Streptococcus pyogenes*, that binds a specific DNA sequence, the *six* site (Alonso et al, 1995, *of record; see pg 2939, Figure 1), is the only species whose complete structure is disclosed. However, the art recognizes an enormous genus of proteins with significant sequence similarity and identity to the beta recombinase encoded by the plasmid pSM19035 *Streptococcus pyogenes* (Accession YP_232767.1 GI:63021996; see Appendix). The art also teaches that resolvase/invertase proteins, of which beta recombinase is a family member, have numerous, dispersed regions of high homology separated by numerous regions of comparatively low homology (Alonso et al, FEMS Microbiology Letters 142(1): 1-10, 1996; pg 4, Figure 1). However, the specification does not disclose any identifying characteristic as to how an artisan would have differentiated beta recombinase from *Streptococcus pyogenes* from any other recombinase from any other prokaryote. Furthermore, neither the art nor the instant specification teach what amino acids are necessary for beta recombinase recombination activity. In regard to beta recombinase from prokaryotic species other than *Streptococcus*

pyogenes, it is noted that the specification does not provide any disclosure whether these sequences from other species would have had the same characteristics or would have had additional characteristics or properties. The only other identifying characteristic to distinguish different members of the claimed genus is that the prokaryotic beta recombinase would perform intramolecular recombination utilizing the recombinase-specific, *six* sites or modified versions (pg 2, lines 29-30; pg 3, line 30). However, neither the art nor the specification teach the complete structure of natural or modified versions of *six* sites recognized by the claimed genus of beta recombinases. As of the filing date of the instant specification, the only art-recognized *six* site (Alonso et al, 1995, *of record; see pg 2939, Figure 1) is recognized only by the beta recombinase encoded by the plasmid pSM19035, derived from *Streptococcus pyogenes*. It is noted that all these beta recombinases vary greatly in structure and recognize different nucleotide sequences where the recombination reaction occurs, and therefore each represents a subgenus. Furthermore, neither the art nor the specification teach what amino acids are necessary to have or to change so as to provide a beta recombinase that has recombination activity upon the modified *six* site (pg 3, line 30). The one species of beta recombinase specifically disclosed, encoded by the plasmid pSM19035 *Streptococcus pyogenes* (Accession YP_232767.1 GI:63021996), is not representative of the genus because the genus is highly variant. Again, the members of any of the subgenuses themselves would have very different structure and the specification does not provide any description of any identifying characteristics of the species of the subgenuses.

With respect to the use of 'specific target sequences', the specification and the art of record clearly teach that beta recombinase can use only the polynucleotide sequences set forth as the *six* site sequence. Presently, in order to practice the invention as claimed the artisan must be in possession of the appropriate target sequence for beta recombinase to bind and effect recombination. The specification describes methods of using beta recombinase and the requirement of target sequences for targeting recombination, however, the only target sequence disclosed is the *six* site. The specification fails to provide any other sequence besides the *six* site sequence as a target sequence for beta recombinase. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicant's effective filing date. Possession may be shown by actual reduction to practice, clear depiction of

the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.*, 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed embodiment of 'specific target sequences' needed to make and use the invention as claimed lack a written description. The specification fails to describe any polynucleotide encompassed in the claims with particularity to indicate that Applicants had possession of the claimed invention beyond the target *six* site sequence. Further, the specification fails to describe methods to establish any other sequence besides the art-recognized *six* site (Alonso et al, 1995, *of record; see pg 2939, Figure 1). The written description of a claim is evaluated on the basis of the claimed invention as a whole. Case law established that the requirement for written description relates to the subject matter defined by the claims. *In re Wright*, 9 USPQ2d 1649 (Fed. Cir. 1989). To this end, while *six* site sequences meet the written description, no other specific sequence which meets the limitation of functioning as a target site for beta recombinase is adequately described or shown to exist. Thus, the specification fails to demonstrate possession of the invention as claimed. The skilled artisan cannot envision the detailed structure of the claimed target sequences except the six site sequence, and thus, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Case law has established that one cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

The Revised Interim Guidelines state, "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. ...In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written Description). Further, *Vas-cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-cath* at page 1116). An applicant

shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 1 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

The claimed invention **as a whole** [emphasis added] is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicant's effective filing date. The Applicant has not provided any description or reduction to practice of introducing a prokaryotic beta recombinase and its specific target sequences into a pathogenic or Gram-positive bacteria. Based on the Applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the genus of beta recombinases encompassed by the claims except for the beta recombinase encoded by the plasmid pSM19035 *Streptococcus pyogenes* (Accession YP_232767.1 GI:63021996). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Accordingly, given that the specification does not teach what is the complete structure of the enormous genus of beta recombinases, nor a single species of the exceptionally broadly-defined "pathogenic and Gram-positive bacteria" genus, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the applicant is in possession of the required starting materials to perform the necessary active steps and effect the claimed method, at the time the application was filed.

Thus, for the reasons outlined above, it is concluded that Claims 29-30 do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

8. **Claims 29-30 are rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the

state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The claims are exceptionally large for reasonably encompassing an enormous genus of beta recombinases extant in an enormous genus of prokaryotic organisms. As commonly understood in the art, a pathogen is a biological agent that causes disease or illness to its host, and includes both Gram-negative and Gram-positive bacteria. The term is most often used for agents that disrupt the normal physiology of a multicellular animal or plant (wikipedia, en.wikipedia.org/wiki/Pathogen, last visited on November 17, 2006), and thus embraces an enormous genus of human and non-human pathogenic prokaryotes.

The inventive concept of the instant claims is the ability to manipulate the genome of pathogenic and Gram-positive bacteria by introducing the beta recombinase encoded by the plasmid pSM19035, derived from *Streptococcus pyogene,* and a nucleic acid comprising the site-specific *six* site upon which beta recombinase acts so as to effect recombination activity in the bacteria.

The art teaches that beta recombinase is a resolvase/invertase and a member of a large family of the Tn3 family of recombinases (Alonso et al; FEMS Microbiology Letters 142(1): 1-10, 1996; pg 4, Figure 1) distinguished by having numerous, dispersed regions of high homology separated by numerous regions of comparatively low homology. The art also recognizes an enormous genus of proteins with significant sequence similarity and identity to the beta recombinase encoded by the plasmid pSM19035 *Streptococcus pyogenes* (Accession YP_232767.1 GI:63021996; see Appendix item provided in Search Notes for an abbreviated search result). The art of record and the specification teach that beta recombinase can mediate an intramolecular recombination event between two target inverted repeats termed *six* sites in the presence of the proper cofactor(s). However a necessary feature of the invention is the requirement of the two *six* sites present in the DNA. Depending on the orientation of the *six* sites, the recombination and resolution of the event results in either deletion or inversion of the sequence between the two *six* sites. However, there is no guidance in the instant specification, nor the art of record, for the use of appropriate vectors, the specific promoter sequences or

cloning details for introducing *six* sites into the enormous genus of bacteria encompassed by the claims. Furthermore, Applicant's specification discloses that "beta recombinase cannot promote intermolecular recombination in bacterial cells" (pg 14, lines 1-2; see also Patent No. 6,780,644 B1, column 8, lines 63-64). Neither the instant specification, nor the art of record, has resolved the many complexities involved in targeting inverted repeat sequences, such as the *six* site sequences, to the gene of interest through homologous recombination in all prokaryotes.

The claims require that beta recombinase be provided to prokaryotic cells. The means or route of administration for providing the beta recombinase is not specifically recited. It is noted that the physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). Transformation methods do exist for some prokaryotic organisms routinely manipulated in the art. For example, Ceglowski et al (Mol. Gen. Genetics 241: 579-585, 1993) teach the introduction of plasmid pSM19035, derived from *Streptococcus pyogenes* and which replicates by the theta-mechanism (pg 579, column 2, line 9), into *Bacillus subtilis*, which the art recognizes to be Gram-positive bacteria (see pg 581, Figure 1). However, this line of experimentation was designed to identify regions of the plasmid necessary for stable propagation of the plasmid, not the instantly claimed methods of manipulating pathogenic and Gram-positive bacteria as contemplated by Applicant. Furthermore, the published method to introduce pSM19035 into *Bacillus subtilis* is not known in the art to be readily transferable to all members of the claimed genus of prokaryotic organisms. Without evidence to the contrary, the means by which different prokaryotic organisms may be transformed and the transcriptional regulatory mechanisms necessary to express the desired transgene are not consistent and varies according to the particular host species. In the instant case, there is no clear teaching on the level of expression of beta recombinase needed to mediate the recombination event between two *six* sites in the genus of prokaryotic organisms. Since the Applicants have not disclosed a means to deliver all the nucleic acids encompassed by the claims to all of the prokaryotes encompassed by the claims, there is no way to predict efficiency of delivery nor expression of an artisan's transgene.

Finally, the specification and the art of record clearly teach that cofactors are strictly required for beta recombinase to mediate a recombination event. As detailed in the specification, the necessity of HU and/or Hbsu from a prokaryotic source is absolute for the resolution of the

recombination event catalyzed by beta recombinase. The Hbsu is required for the resolution and DNA inversion mediated by beta recombinase (Alonso et al, JBC, 1995, * of record, page 2938). Substitution of HU from *E. coli* for Hbsu functions *in vitro* as a chromatin associated protein affecting recombination (Alonso et al, MM, 1995, * of record, page 471), however in the absence of either of these two factors, recombination does not occur (Alonso et al, JBC, 1995, * of record, page 2943). While proteins having similarity to HU or Hbsu may exist in other prokaryotic organisms, the specification and the art of record is silent as to whether such proteins exist and are capable of even functioning with beta recombinase. In fact, the specification discloses that "beta recombinase cannot promote intermolecular recombination in bacterial cells" (pg 14, lines 1-2; see also Patent No. 6,780,644 B1, column 8, lines 63-64). Further, while Hbsu or HU could theoretically be supplied supplementally, the instant methods do not recite such an active step. The specification is silent on the amounts or levels of expression, if supplied as a transgene, of these cofactors which are required to effectively act as cofactors in the genus of prokaryotic organisms encompassed by the claims. The instant specification and the art of record teaches that specific chromatin cofactors are required for beta recombinase activity, however it fails to provide a nexus with the necessary guidance which enables the artisan to supply these cofactors in effective amounts resulting in beta recombinase activity in the claimed prokaryotic genus.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and the state of the art at the time of the claimed invention was made, it would have required one of skill in the art undue experimentation to practice the invention as claimed.

9. **Claims 29-30 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 29 recites the limitation "its" in reference to a specific target sequence. There is insufficient antecedent basis for this limitation in the claim. It is unclear if the term "its" is in reference to the beta recombinase or some endogenous sequence in "pathogenic and Gram-positive" bacteria.

Claims 29-30 are unclear in the recitation of 'its specific target sequences' because the specification and the art of record teach that only the *six* site sequence functions as a target sequence (page 2), and it is unclear what other sequences may function as additional target sequences.

10. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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